REMARKS/ARGUMENTS

The Present Invention

The present invention pertains to compositions comprising a dual specificity lymphocyte or a population thereof and a method of preparing the same.

The Pending Claims

Claims 1, 4, 7, 8, 10, 40, 41, 44-46, 52-61, 71-76, and 79-93 are pending.

Discussion of the Amendments to the Claims

Claim 55 has been amended to address a typographical error, and to provide proper antecedent basis. No new matter has been added by this amendment and support for the amendment is found throughout the specification.

Summary of the Office Action

1. The Office objected to the Information Disclosure Statement submitted on August 25, 2005.
2. The Office commented on the specification.
3. The Office rejected claim 55 under 35 U.S.C. § 112, 2nd paragraph, as allegedly indefinite for failure to particularly point out and distinctly claim the subject that applicant regards as the invention.
4. The Office rejected claims 1, 7, 40, 41, 71, 72, 79-83, 92, and 93 under 35 U.S.C. § 102 as allegedly anticipated by Altenschmidt et al., J. Immunol., 159:5509-5515 (1997).
5. The Office rejected claims 1, 7, 40, 41, 45, 52, 61, 71, 72, 76, 79-83, 87, and 91-93 under 35 U.S.C. § 102 as allegedly anticipated by Beecham et al., J. Immunother. 23:332-43 (2000).
6. The Office rejected claims 1, 7, 8, 40, 41, 45, 46, 52, 56, 58, 61, 71, 72, 75, 76, 79-83, 86, 87, and 90-93 under 35 U.S.C. § 103 as allegedly unpatentable over Beecham et al. in view of Terheyden et al., J. Immunol., 164:6633-9 (2000) and Munz et al., J. Immunol. 162:25-34 (1999).
7. The Office rejected claims 4, 10, 44, 53-55, 57, 59, 60, 73, 74, 84, 85, 88, and 89 under 35 U.S.C. § 103 as allegedly unpatentable over Beecham et al. in view of

Terheyden et al., J. Immunol., 164:6633-9 (2000) and Munz et al., J. Immunol. 162:25-34 (1999), and further in view of Nishimura et al. (U.S. Patent No. 5,830,755).

Information Disclosure Statement

The Office Action alleged that the Information Disclosure Statement (IDS) filed August 25, 2005 failed to comply with 37 C.F.R. § 1.97(c) because it lacked a statement as specified in 37 C.F.R. § 1.97(e). Applicants respectfully traverse the allegation and request that the Examiner consider the documents listed in the IDS, initial the accompanying Form 1449, and return the initialed form to the undersigned.

The IDS was filed after a non-final Office Action, but before a Notice of Allowance or Final Action. 37 C.F.R. § 1.97(c) requires such an IDS to be accompanied by either the 37 C.F.R. § 1.97(e) statement or the fee of $180 set forth in 37 C.F.R. § 1.17(p). Applicants elected the latter option (submitting the fee of $180) as evidenced on pages 2 and 3 of the IDS. Accordingly, it is respectfully submitted that no 37 C.F.R. § 1.97(e) statement is needed, and the IDS should be considered.

Discussion of the Comment on the Specification

The Office Action stated that the status of application 08/547,263, cited on page 17, line 5 of the specification, will need to be updated as necessary. Prosecution is currently suspended in that application. As indicated in earlier correspondence, Applicants will update the specification when appropriate.

Discussion of the Rejection under 35 U.S.C. § 112, Second Paragraph

Claim 55 was rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failure to particularly point out and distinctly claim the subject that applicant regards as the invention. This rejection has been rendered moot by the amendment of claim 55 so as to depend from claim 54. Accordingly, the rejection should be withdrawn.

Discussion of the Rejections under 35 U.S.C. § 102

Claims 1, 7, 40, 41, 71, 72, 79-83, 92, and 93 were rejected under 35 U.S.C. § 102 as allegedly anticipated by Altenschmidt et al., J. Immunol., 159:5509-5515 (1997) (hereinafter

"Altenschmidt"). Applicants respectfully traverse the rejection because the Office Action has failed to establish that Altenschmidt teaches all of the elements of the rejected claims.

"Anticipation under 35 U.S.C. § 102 requires that a single prior art reference disclose each and every limitation of the claimed invention." *Mohn, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 66 USPQ2d 1429 (Fed. Cir. 2003). Accordingly, if the Office Action cannot specifically identify every limitation of a rejected claim in the cited reference, a *prima facie* case of anticipation cannot be established.

Altenschmidt describes the transduction of T cells with chimeric T cell receptor (TCR) genes by polyclonally activiating and co-culturing T cells with retrovirus-producing packaging cells ΩE, the retrovirus carrying a chimeric gene encoding a single chain Ab domain joined to the ζ(zeta)-chain of a T cell receptor (page 5510, left column, paragraph 4).

Of the claims rejected by the Office over Altenshmidt, claims 1, 40, 41, 72, 79, and 81 are independent. Claim 1 is representative of the independent claims for purposes of discussing the failure of Altenschmidt to constitute an anticipatory reference.

Claim 1 recites a composition comprising (A) a T lymphocyte having (i) a recombinant chimeric receptor, which is reactive with a tumor antigen, and (ii) an endogenous T-cell receptor reactive with a cell that is allogeneic to the T lymphocyte, and (B) the cell that is allogeneic to the T lymphocyte. The Office Action provided no evidence to establish that the T lymphocytes of Altenschmidt have an endogenous T-cell receptor reactive with a cell that is allogeneic to the T lymphocyte. The Office Action has also failed to provide any evidence that Altenschmidt teaches both a T lymphocyte and a cell allogeneic to that T lymphocyte. Moreover, the Office Action provided no indication whether Altenschmidt's T cells and packaging cells ΩE are derived from the same species, let alone from genetically different individuals of the same species. For these same reasons, the Office Action has also failed to establish a *prima facie* case of anticipation in view of Altenschmidt for the remaining rejected independent and dependent claims. Accordingly, the rejection is improper and should be withdrawn.

Claims 1, 7, 40, 41, 45, 52, 61, 71, 72, 76, 79-83, 87, and 91-93 were rejected under 35 U.S.C. § 102 as allegedly anticipated by Beecham et al., J. Immunother. 23:332-43 (2000) (hereinafter "Beecham"). Applicants respectfully traverse the rejection because the Office Action has failed to establish that Beecham teaches all of the elements of the rejected claims.

Beecham teaches an expression cassette encoding heavy and light chain variable regions (joined by a flexible linker) from the humanized MN14 antibody fused to the zeta-chain of human TCR, with an intervening CD8α(alpha) hinge region (page 333, right column, last paragraph). This cassette is contained in a retroviral vector that is used to transfect GP-E86 cells, taking the resulting viral supernatant to infect PG-13 cells, which in turn produces viral supernatant that is used to transduce normal human peripheral blood lymphocytes (page 334, left column, first paragraph-continued from previous page). Prior to transduction, the lymphocytes are activated in AIMV media supplemented with IL-2 and OKT3, a mouse antibody (page 334, right column, first full paragraph, as well as left column, first full paragraph, lines 9-12). The transduced T cells are then used in cytotoxicity assays against tumor cell targets (page 334, right column, last paragraph, through page 335, left column).

The same independent claims as rejected over Altenschmidt were also rejected over Beecham: claims 1, 40, 41, 72, and 79. Claims 1 and 41 are representative of the independent claims for purposes of discussing the failure of Beecham to constitute an anticipatory reference.

Claim 1 recites a composition comprising (A) a T lymphocyte having (i) a recombinant chimeric receptor, which is reactive with a tumor antigen, and (ii) an endogenous T-cell receptor reactive with a cell that is allogeneic to the T lymphocyte, and (B) the cell that is allogeneic to the T lymphocyte. With respect to, for example, claims 1, 40, 72, 79, and 82, the Office Action provided no evidence to establish that the T lymphocytes of Beecham have an endogenous T-cell receptor reactive with a cell that is allogeneic to the T lymphocyte.

Claim 41 is directed to preparing lymphocytes having dual specificity comprising: contacting lymphocytes with a cell that is allogeneic to the lymphocytes; and transducing the lymphocytes with a chimeric receptor gene, said gene encoding a chimeric receptor, which is reactive with a tumor antigen. Beecham does not teach such a preparation, which the Office Action admitted on the bottom of page 5. Beecham merely discloses a preparation in which T cells are activated using cell culture, IL-2 and a mouse antibody followed by viral supernatant for transduction. Moreover, Beecham does not disclose a preparation of T lymphocytes involving the addition of modified T lymphocytes to tumor cultures, which, as stated above, the Office Action admits. By the point Beecham adds modified T lymphocytes to tumor cultures, the lymphocytes have already been prepared and the addition is for

purposes of killing tumor cells (*see*, description of Beecham's Cytotoxicity Assays, end of left column of page 334 through right column of page 335). For these reasons, the Office Action also failed to establish a *prima facie* case of anticipation in view of Beecham for the remaining rejected dependent claims. Accordingly, it is respectfully submitted the rejection is improper and should be withdrawn.

Discussion of the Rejections under 35 U.S.C. § 103

Claims 1, 7, 8, 40, 41, 45, 46, 52, 56, 58, 61, 71, 72, 75, 76, 79-83, 86, 87, and 90-93 were rejected under 35 U.S.C. § 103 as allegedly unpatentable over Beecham in view of Terheyden et al., J. Immunol., 164:6633-9 (2000) (hereinafter "Terheyden") and Munz et al., J. Immunol. 162:25-34 (1999) (hereinafter "Munz"). Applicants traverse the rejection and respectfully request that it be withdrawn.

> To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).
>
> A reference should be considered as a whole, and portions arguing against or teaching away from the claimed invention must be considered. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 230 USPQ 416 (Fed. Cir. 1986).

The deficiencies of Beecham have been discussed above. Terheyden and Munz do not remedy the deficiencies of Beecham either alone or in combination. The Office Action did not show that Beecham, Terheyden or Munz disclose any particular T lymphocyte that contains both a recombinant chimeric receptor reactive with a tumor antigen but also a second receptor, the second receptor reactive with a cell that is allogeneic to the T lymphocyte. Accordingly, the Office Action failed to establish at least the third prong of the

test for a *prima facie* case of obviousness. That failure alone is sufficient to prevent the Office from establishing a *prima facie* case of obviousness.

The Office Action also failed to show a suggestion or motivation to combine the references, and does so by its own admission (on page 5) that Beecham differs from the instant claims in that Beecham's T cells are activated in a "special" medium and fails to teach a composition comprising allogeneic monocytes such as dendritic cells or other antigen-presenting cells. One of skill in the art would not need to look beyond Beecham, *e.g.*, to the use of allogeneic or autogenic cells, because Beecham's special medium is specific, effective, and sufficient for producing, activating, and proliferating T cells. This "special" medium is described on page 334, right column, in the first paragraph under the heading "Lymphocyte Transduction and Culture." The "special" medium includes AIMV media supplemented with 100 U/mL IL-2 and 20ng/mL OKT3.

Beecham states: "treatment with OKT3 induces rapid T-cell proliferation. This selective T-cell proliferation quickly leads to cultures that are virtually 100% T cell in origin and effectively eliminates the influence of any contaminating cells from subsequent assays." With such an effective method, there is neither suggestion nor motivation to look toward other techniques such as those described in Terheyden and Munz. Moreover, the Office Action merely assumed and failed to demonstrate that the addition of autogenic or allogeneic cells to the "special" medium would have a positive effect and not interfere with the underlying effectiveness of the medium. In so doing, the Office Action also failed to establish a reasonable expectation of success. Furthermore, and as discussed above, the Office Action's description of Beecham as differing from the claims as merely a failure to teach a composition that comprises allogeneic monocytes is an incomplete rendering of the deficiencies of Beecham.

In describing Terheyden, the Office Action alleged that Terheyden establishes that it was well known in the art that co-culturing monocytic antigen-presenting cells with T lymphocytes has been widely used for T cell expansion, activation, or as a tool for functional investigation. However, the Office Action failed to indicate where in Terheyden this is established. Terhedyen discloses general information about the understanding of immune system molecules and their effects. There is no teaching in Terheyden that it was well known in the art that co-culturing monocytic antigen-presenting cells with T lymphocytes had been widely used for T cell expansion, activation, or as a tool for functional investigation.

The Office Action also failed to account for all the differences and consequently improperly trivializes the differences between what Terheyden teaches and what is currently claimed. Apart from culturing T cells with other cells, which the Office Action admitted are autogenic and not allogeneic, the Office Action has not established whether or how Terheyden teaches all the elements of the claims either alone or in combination with the other cited references.

The Office Action alleged that Munz illustrates that allogeneic stimulus is "more powerful" in obtaining potent CTL cells compared to autologous stimulation, but fails to point to where, if anywhere, in Munz such a teaching occurs. An analysis of Munz demonstrates, if anything, the opposite of the Office Action's conclusion. For example, in the abstract, Munz states: "Peptide library-specific allorestricted CTL were found to constitute up to half the allorestrictive CTL response and occurred at **twofold *lower* frequency than autologous** peptide library-specific CTL" (emphasis added).

Moreover, at the bottom of page 28, left column, Munz states: "Thus, the repertoire of PBL contains approximately twice the amount of self-restricted CTL as allorestricted CTL." In making its conclusions, Munz states: "These allorestricted CTL showed reactivity toward foreign as well as self peptides (e.g., 30F7). In addition, the recognition of foreign MHC plus peptide was similar in specificity and avidity to conventional self MHC-restricted T cell recognition. Similar data for mice have recently been obtained (51)" (page 32, right column, last full paragraph). Accordingly, Munz teaches that self restricted lymphocytes yield better results, or in the least, similar results, compared to allorestricted lymphocytes. By doing so, Munz teaches against a combination with Beecham and/or Terheyden and away from the presently claimed invention.

Claims 4, 10, 44, 53-55, 57, 59, 60, 73, 74, 84, 85, 88, and 89 were rejected under 35 U.S.C. § 103 as allegedly unpatentable over Beecham in view of Terheyden and Munz, and further in view of Nishimura et al. (U.S. Patent No. 5,830,755) (hereinafter "Nishimura"). Applicants traverse the rejection and respectfully request that it be withdrawn.

The Office Action stated that Nishimura supplements the deficiencies of the other cited references by teaching a chimeric receptor specific for an ovarian tumor antigen, preferably Mov-γ, and that transduced T cell recited in the claims were well known in the art. However, such a teaching is not sufficient to remedy the deficiencies of the other references as discussed above. Applicants have discussed Nishimura in several past Replies to Office

Action in this application, *e.g.*, Applicants' reply of August 25, 2005, pages 10-11. The Office has yet to provide evidence that the cells taught by Nishimura necessarily have a T cell receptor reactive with an allogeneic cell as claimed.

All the claims rejected over the Nishimura and the other references are dependent claims. Because Nishimura cannot remedy the deficiencies of the other references in respect to the independent claims, it follows that Nishimura cannot remedy the deficiencies of claims from which they depend. Accordingly, the rejection is improper and should be withdrawn.

In citing Nishimura in the rejection, the Office Action cited a 61 column long patent, and the most specific citation to Nishimura is to Example 4, which itself is over 4 columns long. This level of specificity puts an improper burden on the Applicants. 37 C.F.R. § 1.104(c)(1) requires that the Examiner, when rejecting a claim for want of novelty or for obviousness, must not only cite the best references at the Examiner's command but also must designate the particular part relied upon as nearly as practical for complex references. The Examiner is also obligated to provide Applicants with a sufficiently detailed explanation of the relevance of the particular part relied on. It is respectfully submitted that the Office Action has neither designated the particular part relied upon nor provided a sufficiently detailed explanation of its relevance.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

Jeremy M. Jay, Reg. No. 33,587
LEYDIG, VOIT & MAYER
700 Thirteenth Street, N.W., Suite 300
Washington, DC 20005-3960
(202) 737-6770 (telephone)
(202) 737-6776 (facsimile)

Date: 27 June 2006